DETAILED ACTION

Status of Application/Amendment/Claims

Applicant's response filed 08/18/2011 has been considered. Rejections and/or objections not reiterated from the previous office action mailed 04/18/2011 are hereby withdrawn. The following rejections and/or objections are either newly applied or are reiterated and are the only rejections and/or objections presently applied to the instant application. The text of those sections of Title 35, U.S. Code not included in this action can be found in a prior Office action.

With entry of the amendment filed on 08/18/2011, claims 1-8, 11, 19 and 58-60 are pending and currently under examination in the application.

Response to Arguments

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

The rejection of claims 1 -8, 11, 19 and 58-60 under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement is maintained for the reasons of record.

Applicants have further amended the claim to define the gene silencing effector is an RNA capable of silencing a target gene. This description is further introduction of new matter. As stated previously, the specification does not define what an effector is

nor does the specification disclose any language describing "a gene silencing effector" and defining the effector as being "RNA capable of silencing a target gene" is new matter. This limitation is limiting the effector to an RNA capable of silencing a target gene however the only RNA described in the specification with gene silencing capability is a siRNA or a small hairpin-like RNA neither of which are defined as a gene silencing effector.

If Applicant believes that such support is present in the specification and claimed priority documents, Applicant should point, with particularity, to where such support is to be found.

Claim Rejections - 35 USC § 112

The rejection of claims 1 -8, 11, 19 and 58-60 under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement is withdrawn.

New Rejections and Objections

Claim Objections

Claim 8 is objected to because of the following informalities: claim 8 recites "capable of silencing a target gene released in a eukaryotic cell" and it appears the sentence is missing the word "when" between gene and released to indicate the RNA is released in the cell. Appropriate correction is required.

Claim Rejections - 35 USC § 103

The scope of the claimed invention was considered further which led to the new grounds of rejection below.

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

Claims 1 -8, 11, 19 and 58-60 are rejected under 35 U.S.C. 103(a) as being unpatentable over Abrams et al. (J. Biol. Chem 264(24):14016-14021, 1989), Lau et al. (Science 294:858-862, 2001), Mitchell et al. (of record cited on form 892 mailed 03/11/2008), Krawczak et al. (Hum Genet 1992, Vol. 90: 41-54 of record PTO Form 892 mailed 03/11/2008), Zhuang et al. (PNAS Vol. 86: 2752-2756 of record PTO Form 892 mailed 03/11/2008), Coolidge et al. (of record cited on 892 mailed 01/23/2009), Bennett et al. (US Patent No. 6,710,174) and Davey et al. (J. Cell Science 112: 4663-4672, 1999 of record cited on 892 fled 07/22/2010).

The claims are drawn to an isolated RNA comprising an artificial intron containing a gene silencing effector wherein said gene silencing effector is an RNA capable of silencing a target gene when released in a cell, wherein the artificial intron RNA contains a splice donor, acceptor, branch site and a poly-pyrimidine tract as claimed.

For purposes of applying prior art, the isolated RNA is not limited to being produced from any particular expression system. The claims at their broadest are

drawn to any RNA capable of being released in a cell and capable of silencing a target gene i.e. inhibiting the expression of a target gene.

Abrams et al. teach a recombinant nucleic acid composition comprising at least a nucleic acid flanked by exons wherein said nucleic acid intron can be cleaved out of the exons.

Abrams et al. do not teach the intron is a gene silencing effector that is capable of inducing gene silencing however Abrams et al. state they are examining the potential of the system for its ability to overproduce stable antisense RNAs capable of diminishing the product of unlinked genes (see pg 14020, col. 2, last sentence) thus providing motivation to use this expression system for generating molecules that are capable of silencing target gene expression.

At the time of the invention Lau et al. taught identification of gene-silencing RNAs (microRNAs) that exist within an intron of protein-coding exons (page 860, Table 1) in C. elegans. Thus at the time of the invention, one of ordinary skill in the art was aware of the scientific concept that gene silencing RNA molecules may be encoded within at least one intron of a protein-coding gene flanked by exons and were aware that gene silencing RNAs such as microRNAs had important regulatory roles in cells and would have been motivated to use these RNAs as gene silencing molecules.

It would have been obvious to one of ordinary skill in the art to substitute the intron encoding a nucleic acid with an intron-encoded gene silencing RNA art taught by Lau et al. with a reasonable expectation of success.

Mitchell teach an efficient splice acceptor site having the sequence of CCACAGC (see column 12, lines 15-20) that is capable of efficiently splicing pre-mRNA along with branch sites, donor sites and polypyrimidine tract sequences.

Krawczak et al. teach a 5' splice donor site having a sequence that contains AAGTAAGT (see page 41).

Zhuang et al. teach a preferred branch site sequence for mammalian mRNA splicing having the sequence UACUAAC (see page 2752).

Coolidge et al. teach the polypyrimidine tract is essential in pre-mRNA splicing and teach the sequence of the polypyrmidine tract is flexible but for efficient splicing, the tract must contain a threshold of 8 uridine residues (see pages 888-889).

Bennett et al. teach exon regions are preferred target sites for inhibitory nucleic acid molecules (see at least column 7) and Davey et al. teach reduced expression of integrin B1 prevents cell proliferation thus providing a motivation to target this gene in cells (see entire reference).

It would have been obvious to incorporate the acceptor site taught by Mitchell, the 5' donor splice site taught by Krawczak et al. and the branch site sequence taught by Zhuang et al. into the DNA template or isolated RNA comprising an intron RNA taught by Mitchell. It would have been further obvious to incorporate a polypyrmidine tract as claimed.

One of skill in the art would have been motivated to incorporate the acceptor site taught by Mitchell as it is shown this site efficiently allow proper splicing of therapeutic pre-mRNA sequence and one would have wanted to use the 5' donor splice site

because Krawczak et al. teach the efficiency of splicing is critically dependent upon the accuracy of cleavage and rejoining and given this splice donor sequence has been identified as a consensus sequence for splicing, one would have wanted to use the most effective sequence to allow accurate splicing activity in cells to release the sequence as taught by Abrams. One of skill in the art would have been further motivated to use the branch site sequence taught by Zhuang et al. because Zhuang et al. demonstrated that this sequence is preferred in mammalian cells for accurate splicing of mRNA sequence. Given Coolidge et al. teach the sequence of the polypyrimidine tract is flexible but must contain at least a threshold of eight uridines; it would have been a matter of routine experimentation to the skilled artisan to construct and test polypyrimidine tracts that would contain the claimed sequence and incorporate the optimal sequence into the claimed RNA. Moreover, it is well known in the art that exon regions are preferred target sites for inhibitory nucleic acid molecules as taught by Bennett et al. and it would have been obvious to target said region.

Finally, one would have expected to be able to incorporate the sequences taught by Mitchell et al., Krawczak et al. and Zhuang et al. into the DNA template for the isolated RNA given both demonstrate that each sequence is capable of mRNA splicing and further teach said sequence is the preferred sequence for accurate splicing of mRNA in cells. One would have expected to be able to make and find the optimal polypyrimidine tract because Coolidge et al. teach how to make the optimal composition.

Thus in the absence of evidence to the contrary, the invention as a whole would have been *prima facie* obvious to one of ordinary skill in the art at the time the invention was made.

Double Patenting

The nonstatutory double patenting rejection is based on a judicially created doctrine grounded in public policy (a policy reflected in the statute) so as to prevent the unjustified or improper timewise extension of the "right to exclude" granted by a patent and to prevent possible harassment by multiple assignees. See *In re Goodman*, 11 F.3d 1046, 29 USPQ2d 2010 (Fed. Cir. 1993); *In re Longi*, 759 F.2d 887, 225 USPQ 645 (Fed. Cir. 1985); *In re Van Ornum*, 686 F.2d 937, 214 USPQ 761 (CCPA 1982); *In re Vogel*, 422 F.2d 438, 164 USPQ 619 (CCPA 1970);and, *In re Thorington,* 418 F.2d 528, 163 USPQ 644 (CCPA 1969).

A timely filed terminal disclaimer in compliance with 37 CFR 1.321(c) may be used to overcome an actual or provisional rejection based on a nonstatutory double patenting ground provided the conflicting application or patent is shown to be commonly owned with this application. See 37 CFR 1.130(b).

Effective January 1, 1994, a registered attorney or agent of record may sign a terminal disclaimer. A terminal disclaimer signed by the assignee must fully comply with 37 CFR 3.73(b).

Claims 1 -8, 11, 19 and 58-60 are provisionally rejected under the judicially created doctrine of double patenting over claims 1, 10, 14-16, 19-28, 32-41, 43-45 and 47-53 of copending Application No. 11/278,143.

This is a provisional double patenting rejection since the conflicting claims have not yet been patented. Although the conflicting claims are not identical, they are not patentably distinct from each other because the instant claims and the claims of the patent are drawn to patently indistinguishable subject matter.

The claims of copending Application '143 are drawn to methods of inducing intron-mediated silencing in an animal and it would have been obvious to use the

artificial intron of the instant application. Thus the claims are not patentably distinct from each other.

Conclusion

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Kimberly Chong whose telephone number is 571-272-3111. The examiner can normally be reached Monday thru Friday between 7-4 pm.

If attempts to reach the examiner by telephone are unsuccessful please contact the SPE for 1635 Heather Calamita at 571-272-2876. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

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